Feasibility of Treating Post-Transplantation Minimal Residual Disease in Children with Acute Leukemia

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A B S T R A C T

Outcomes are poor for patients with hematologic malignancies who experience overt relapse after allogeneic hematopoietic stem cell transplantation (HCT). Data on outcomes of post-transplantation minimal residual disease (MRD) are limited. In this single-institution, retrospective cohort analysis of children with acute leukemia and myelodysplastic syndrome, we document the pattern of relapse with a primary focus on outcomes of post-transplantation MRD. Forty of 93 patients (43%) who underwent a first allogeneic HCT and had systematic pretransplantation and post-transplantation MRD evaluations at +30, +60, +90, +180 days and +1 and +2 years post-transplantation experienced relapse. The median time to relapse was 4.8 months post-transplantation, with a median survival of 4 months post-relapse. Despite frequent, systematic, routine post-HCT disease restaging evaluation, 31 patients (78%) presented with overt disease at the time of relapse. Seven patients with acute leukemia who had post-transplantation MRD presented at a median of 1 month post-transplantation. Owing to rapid disease progression or treatment-related mortality, there was no improvement in survival in those patients whose leukemia was detected in a state of MRD post-transplantation. Our results suggest that early intervention strategies targeting post-transplantation MRD for relapse prevention in acute leukemia may not be feasible.

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INTRODUCTION

Relapse is the primary cause of treatment failure in patients with hematologic malignancies who undergo allogeneic hematopoietic stem cell transplantation (HCT) [1]. Once patients have relapsed after HCT, treatment options are limited, and the outlook is generally poor [2-7]. One potential approach to improving post-transplantation outcomes involves preemptive interventions for relapse prevention. Treatment of post-transplantation minimal residual disease (MRD; defined as <5% bone marrow blasts or positive cytogenetic or molecular markers of disease) to prevent overt relapse may be one such strategy [8,9].

The majority of previous studies evaluating post-transplantation relapse in acute leukemia are based on patients presenting with overt morphological relapse or high disease burden, in whom outcomes are poor [3,4,6]. However, with frequent post-transplantation surveillance and more sensitive measures of detection, in theory disease recurrence could be detected both earlier and at a state of lower disease burden that may be more amenable to treatment, potentially leading to improved outcomes [10-12]. Certainly, preemptive immunotherapy in the setting of mixed chimerism has shown promise in relapse prevention [13-16]. In addition, treatment of MRD using donor lymphocyte infusion (DLI) in the setting of chronic myelogenous leukemia (CML) before hematologic relapse has lead to durable remissions [17-19]. Outcomes with DLI for treatment of acute leukemia are quite variable, however [20-22]. Data on the outcomes of post-transplantation MRD specifically in the setting of acute leukemia are limited [21,23-26].

In this study, we describe the presentation and management of children with hematologic malignancies who experience post-transplantation relapse. With a focus on understanding the pattern of relapse, the goal was to determine whether post-transplantation MRD is amenable to intervention for relapse prevention.

METHODS

Patients and Inclusion Criteria

This was a single-institution, retrospective cohort study of pediatric patients (age ≤21 years) who relapsed after having undergone a first allogeneic HCT for a hematologic malignancy between January 1, 2003, and December 31, 2010, at The Johns Hopkins Hospital. This cohort included all patients with a diagnosis of acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), mixed phenotypic acute leukemia (MPAL), or lymphoblastic lymphoma (LBL) irrespective of disease status, pretransplantation conditioning, donor and stem cell source, HLA matching, or any other transplant-related variables. Patients with other types of leukemia, including blast crisis CML, were excluded. For this analysis, 1 patient with LBL was analyzed with the patients with ALL. This study was approved by The Johns Hopkins Hospital's Institutional Review Board.

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Disease Monitoring, Surveillance, and Definitions

All patients underwent pretransplantation disease evaluation. Routine post-transplantation surveillance was performed at 30, 60, 90, and 180 days ± 10 days and 1 year and 2 years ± 1 month post-transplantation and as clinically indicated thereafter. Evaluation was disease-specific and included evaluation of chimerism (peripheral blood and bone marrow) and flow cytometry, cytogenetic, and molecular MRD studies (eg, *bcr/abl* in Philadelphia chromosome–positive ALL) from the bone marrow. In addition, lumbar punctures were routinely performed at the foregoing time points to assess central nervous system (CNS) status in all patients.

The day of relapse after HCT was defined as the first day of laboratory confirmation of disease presence, inclusive of post-transplantation MRD. In patients with ALL, MRD was assessed in our central reference laboratory using flow cytometry methods as described previously [27]. Following definitions published by Leung et al. [28], MRD was positive at a level ≥0.01%. For AML, the sensitivity for routine flow cytometry analysis ranged from approximately 0.1% to 1% of cells, depending on the phenotype of the initial leukemia. Treatment-related mortality (TRM) was defined as death unrelated to progressive disease and included transplantation-related mortality or death due to treatment of post-transplantation relapse.

Statistical Analysis

The primary endpoint was overall survival after post-transplantation relapse. Overall survival was defined by the date of relapse until the date of death, censored at the last follow-up date for patients who were alive at the time of this analysis. Probabilities of survival were evaluated using the Kaplan-Meier method. The cumulative incidence of relapse, adjusted for the competing risk of death from TRM, was calculated using the method of Gooley et al. [29]. The *t* test for numerical variables and Fisher's exact test for categorical variables were used to test for differences in characteristics between patients who relapsed and those who did not relapse. Analysis of variance was used to analyze the differences among the various presentations of post-transplantation relapse, specifically by the time to relapse. The level of statistical significance was set at $P < .05$. Statistical analyses were performed with Stata/IC version 12.0 (StataCorp, College Station, TX).

RESULTS

Patient and Relapse Characteristics

Forty of 93 pediatric patients (43%) who underwent a first allogeneic HCT for acute leukemia or MDS relapsed after HCT. Patient characteristics are summarized in Table 1. This number included 21 relapses among 57 patients (37%) with ALL or AML who were in morphological remission and underwent a myeloablative transplantation (Table 2). The cumulative incidence of post-HCT relapse, accounting for the competing risk of transplantation-related mortality, was 17% at 3 months, 26% at 6 months, 37% at 12 months, and 41% at 24 months (Figure 1). This included 41 patients with AML (18 of whom relapsed), 34 with ALL (16 of whom relapsed), 10 with MPAL (4 of whom relapsed), and 8 with MDS (2 of whom relapsed).

At the time of relapse, the majority of patients (n = 31; 78%) presented with morphological (>5% disease) relapse. Twenty-two patients (56%) had clinical signs and symptoms consistent with relapse, including presentation with peripheral blasts, extramedullary disease, cytopenias prompting disease evaluation, and/or other symptoms concerning for disease recurrence (eg, pain). Specifically, 3 patients had leukemia cutis or chloromatous masses, and 1 patient presented with a testicular mass that prompted further evaluation. Eight patients (21%) were asymptomatic, with relapse discovered at prespecified routine disease evaluations, including 2 patients with isolated CNS relapse. Nine patients (23%) presented with post-transplantation MRD that was detected on routine surveillance, including 7 patients with leukemia and 2 with MDS. Details regarding the presentation of relapse were not available for 1 patient with confirmed morphological relapse.

The median time to relapse for all patients was 4.8 months (range, 0.1 to 57 months) post-transplantation. There was a statistically significant difference in the time to relapse by presentation; patients with MRD-positive relapse (n = 9) presented at a median of 1 month post-HCT, those with evidence of disease detected by routine surveillance (n = 8) presented at a median of 3 months post-HCT plant, and those with overt relapse (n = 22) presented at a median of 7.5 months post-HCT ($P < .001$) (Figure 2). After patients with refractory disease were excluded, the median time to relapse for patients with AML and ALL was 4.5 months (range, 1 to 15.8 months) for patients with AML (n = 12) and 6 months (range, 1 to 29 months) for those with ALL (n = 14).

Management of Relapse

Decisions regarding the treatment of relapse varied and were based on the timing of relapse, the patient's condition, and physician and patient/family preference. Six patients received only supportive care, including hospice, palliative, or complementary medicine. In 3 patients, immunosuppressive therapy was withdrawn in response to MRD detection. Twenty-four patients received cytotoxic and/or radiation therapy, and 13 received DLI (with or without previous chemotherapy). Eleven patients were able to proceed to a second allogeneic HCT after attaining remission.

Overall Survival after Post-Transplantation Relapse and Nonrelapse Mortality

Overall survival (OS) was 30% at 6 months, 17.5% at 1 year, 15% at 2 years, and 11% at 5 years post-relapse. Median survival after relapse was 4 months (range, 0.1 to 33 months). Five of 40 patients (12.5%) are currently alive at a median follow-up of 39 months, including 2 patients who continue to be treated for active disease. One survivor had MDS and presented with MRD alone; the remaining 4 survivors presented with overt disease, including 3 with ALL and 1 with MPAL.

Death post-relapse was due to a various causes. The majority of patients died with progressive disease (n = 28). None of the 18 patients with AML survived after post-transplantation relapse. Survival did not appear to differ by therapeutic approach to relapse, with the exception of those who underwent a second HCT. The 3-year overall survival probability among the 11 patients who underwent a second transplant was 27% (95% confidence interval [CI], 6.5% to 54%), compared with 5.4% (95% CI, 0 to 20%) for those who did not ($P = .02$). The patients who proceeded to a second transplantation more often had a later relapse (median time to relapse, 8 months [range, 1 to 29 months]) than those who did not undergo a second transplantation (median time to relapse, 3.8 months [range, 1 to 58 months]). Eight patients died from TRM related to the second transplantation, including 3 patients who developed grade IV acute graft-versus-host disease (GVHD). Three patients remain long-term survivors following second transplantation.

Outcomes of Post-Transplantation MRD

All 9 patients who presented with post-transplantation MRD were discovered on routine planned surveillance. These patients presented at a median of 1-month post-transplantation (range, 1 to 6 months), with 8 exhibiting some evidence of pretransplantation disease. Among the 7 patients with leukemia, 5 had very rapid progression of disease to overt relapse, at a median of 21 days (range, 13 to 24 days) from detection of MRD despite intervention in response to MRD, including early withdrawal of immunosuppression (n = 3) and DLI (n = 2) (Table 3). All patients

Table 1
Characteristics of Pediatric Patients Undergoing First Allogeneic HCT for Acute Leukemia Compared with the Subset Who Relapsed after HCT

Variable	All Patients (n = 93), n (%)	Patients Who Relapsed Post-HCT (n = 40), n (% of All Patients)	*P* Value*
Median age at HCT, years (range)	10 (0.6-21.2)	9 (0.7-20.2)	NS
Male sex	62 (67)	29 (47)	NS
Diagnosis			
AML	41 (44)	18 (44)	NS
ALL	34 (37)	16 (47)	
MPAL	10 (11)	4 (40)	
MDS	8 (9)	2 (25)	
Disease status at HCT, by disease			
AML			
Active disease	8 (9)	5 (63)§	<.01†
MRD + CR	13 (14)	6 (46)	
MRD Neg CR	20 (22)	7 (35)	
ALL			
Active disease	1 (8)	1 (100)	
MRD + CR	13 (14)	8 (62)	
MRD Neg CR	20 (22)	7 (35)	
MPAL			
Active disease	1 (8)	1 (100)	
MRD + CR	1 (8)	0 (0)	
MRD Neg CR	8 (9)	3 (38)	
MDS	8 (9)	2 (25)	
Performance Status at HCT			
80-100%	84 (90)	33 (39)	.02
40-70%	8 (9)	6 (75)	
Indication for HCT (for leukemia patients only; n = 85)			
Primary induction failure	12 (13)	6 (50)	NS
High-risk disease‡	24 (26)	6 (25)	
Relapsed disease	25 (27)	10 (40)	
Multiple indications	24 (26)	16 (67)	
Remissions (for leukemia patients only, n = 85)			
CR1	41 (44)	16 (39)	NS
CR2	27 (63)	12 (44)	
CR3+	7 (9)	4 (57)	
Refractory	10 (11)	7 (70)§	
HCT conditioning regimen			
Myeloablative	79 (85)	30 (38)	<.01
Reduced intensity	14 (15)	10 (71)	
Stem cell source			
Bone marrow	71 (76)	34 (48)	NS
Single cord blood	18 (19)	6 (33)	
Double cord blood	1 (1)	0 (0)	
Peripheral blood	3 (3)	0 (0)	
Donor type			
Matched sibling	26 (28)	11 (42)	NS
Matched unrelated	30 (32)	12 (40)	
Cord blood	19 (20)	6 (32)	
Haploidentical‖	15 (16)	9 (60)	
Mismatched related/unrelated	3 (3)	2 (67)	

HCT indicates hematopoietic stem cell transplantation; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MPAL, mixed phenotypic acute leukemia; MDS, myelodysplastic syndrome; MRD, minimal residual disease; CR, complete remission; NS, not significant.
Active disease defined by >5% blasts, including those with refractory disease. MRD includes patients with levels >0.01% by flow cytometry for ALL and > 0.1% for AML/MPAL, or detectable disease by cytogenetics.

* Log-rank *P* value for comparison of relapse-free survival (relapse versus no relapse).

† *P* value is in comparison of relapse-free survival for those with active disease to those in CR.

‡ High-risk determination was made by transplant physician using a constellation of multiple assessments, which included cytogenetics (eg, monosomy 7, hypodiploid <43 chromosomes, FLT3/ITD), end-induction MRD positivity and/or phenotype (MPAL) and in conjunction with standard accepted criteria for transplant indications.

§ Two patients with refractory disease before HCT died from early TRM before day +100. One patient with refractory AML remains a long-term survivor post-HCT without relapse.

‖ Many patients who received the initial haploidentical transplants were on an institutional nonmyeloablative protocol, which also included patients with active disease at the time of HCT.

received disease-directed therapy, with the exception of 1 patient who died from early TRM at day +118 post-HCT with rising levels of MRD at the time of death. All patients who received disease-directed therapy died from TRM, with the exception of 1 patient with MDS who presented with MRD based on evidence of cytogenetic relapse at day +180 post-transplantation and received DLI before further disease progression occurred. This patient remains a long-term survivor. Survival of patients who presented with MRD post-transplantation was no better than that in patients who presented with frank relapse, despite preemptive interventions for MRD.

DISCUSSION

Despite the hypothesis that treatment of post-HCT MRD may represent a window of opportunity for relapse prevention and thereby improve outcomes, our findings do not support this as an optimal strategy for relapse prevention in

Table 2
Relapse Rate and Time to Relapse for Patients with ALL and AML in a Morphological Remission at HCT who Underwent a Myeloablative Preparative Regimen, by Pre-HCT MRD Status

Disease	Pre-HCT MRD Status	Total Patients	Number of Patients Experiencing Relapse at or before the Planned Restaging Evaluation Time Points						Total Relapses	Crude Relapse Rate, %	Median Time to Relapse, d
			Day 30	Day 60	Day 90	Day 180	Day 365	Day 365+			
ALL	Negative	20	1	0	1	2	1	2	7	35	182
	Positive	11	0	3*	0	1	3	0	7	64	132
AML	Negative	15	0	0	0	0	2	1	3	20	238
	Positive	11	0	0	0	2	1	1	4	36	224

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; HCT, hematopoietic stem cell transplantation; MRD, minimal residual disease. MRD considered positive when <5% and ≥0.01% in ALL and ≥0.1% in AML.
* Two patients presented with post-HCT MRD.

patients with acute leukemia. One critical observation is that despite the frequent monitoring, the majority of patients (78%) who experienced relapse had already progressed to morphological relapse by the time of disease detection. Moreover, in patients with disease detected in a state of MRD, disease progression was often rapid, detected early post-transplantation or identified at a time when ongoing toxicities compromised the efficacy of therapeutic interventions.

With the ability to monitor for much lower levels of disease burden using techniques that greatly increase the sensitivity of disease detection [11], post-transplantation MRD monitoring was performed at frequent, accepted standard intervals at our center. Considering this rigorous and multimodal routine post-transplantation evaluation, including complete data from all disease evaluation time points with disease assessment by flow cytometry (with ALL MRD analysis performed at our central reference laboratory), molecular, and chimerism studies, the finding that the vast majority of patients still presented with morphological relapse was unexpected. This was especially notable in the patients with ALL and AML who were in a morphological remission at the time of transplantation and received a myeloablative transplant. In this subgroup, only 2 of 21 patients who relapsed presented with post-transplantation MRD before morphological relapse.

A possible explanation for this finding may be related to the timing of disease recurrence in relation to the timing of disease evaluation. In this study, the median time to relapse was 4.8 months post-transplantation, between the 3-month and 6-month scheduled evaluations. This suggests that adding an evaluation between 3 and 6 months may aid earlier detection of MRD before morphological relapse. Similarly, in a recent study of post-HCT MRD in ALL, Zhao et al. [26] they also noted that MRD was not detected before hematologic relapse in the patients who relapsed between 3 and 6 months, suggesting the need for additional evaluation during this period. At our center, we continue to perform frequent MRD surveillance, and often add an additional MRD evaluation between the 3- and 6-month evaluations and another at around 9 months post-transplantation for patients with high-risk disease.

The sensitivity of disease detection methods may be an important consideration as well. Balduzzi et al. [21], in a recent study evaluating pre- and post-HCT MRD in patients with ALL using real-time quantitative polymerase chain reaction methods, demonstrated that intervention for low-level post-transplantation MRD ($<1 \times 10^{-4}$) can prevent overt relapse. However, in their study, all those with higher-level MRD ($\geq 1 \times 10^{-3}$) and those who experienced a 1-log increase in MRD (albeit still at low levels), all ultimately experienced overt relapse despite preemptive interventions. In our cohort, 4 patients with AML relapse had higher-level MRD, and those with ALL progressed rapidly. This suggests the need for a more sensitive method of disease detection in

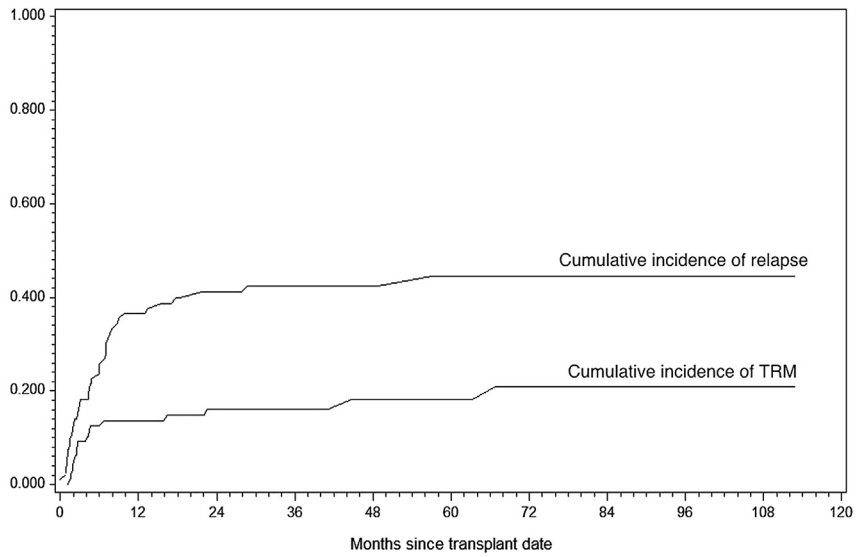

Figure 1. Cumulative incidence of relapse and TRM analyzed at competing risks starting at the date of HCT for 93 consecutive patients who underwent a first allogeneic HCT for acute leukemia or MDS.

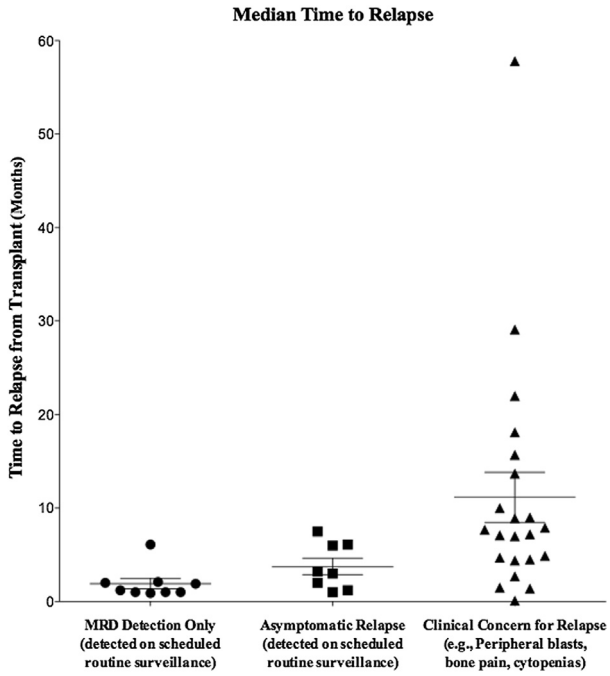

Figure 2. Median time to relapse, by relapse presentation. Routine marrow evaluation was performed for all pediatric patients at approximately days +30, +60, +90, and +180 and years +1 and +2 post-HCT. Analysis of variance was used to analyze the differences in the time to relapse by the various presentations of post-HCT relapse. The middle line in the boxplot indicates the median, with whiskers indicating top and bottom quarter percentiles ($P < .001$).

the post-transplantation setting, where there may be prognostic implications of very low levels of disease; however, this strategy might not be useful for predicting extramedullary relapse, which might not be reliably detected with bone marrow monitoring [21,26,30]. Six patients in our cohort presented with extramedullary relapse as the first manifestation of disease recurrence without previous marrow disease involvement.

Even with more frequent monitoring and more sensitive measures of disease detection, whether these measures would improve outcomes for the majority of patients with post-transplantation relapse is uncertain, given the ability to treat only very low levels of disease and the potential for rapid disease progression. In our study, the median time of disease progression from the detection of post-transplantation MRD to overt relapse was relatively short (median, 21 days), with other studies reporting times to overt relapse of 1 to 3 months after detection of MRD [26]. Immunotherapeutic approaches to induce a graft-versus-leukemia effect with early withdrawal of immunosuppression or DLI may be beneficial and most effective in patients with early relapse and low disease burden, but may require weeks to take effect and have limited efficacy in the setting of rapid disease progression or higher disease burden [21,31,32]. Moreover, this might not be an option in those with pre-existing GVHD [13,33-37]. Disappointingly, in our study, similar to other reports [5,21,32,38], the use of DLI, even preemptively, was not associated with long-term survival in patients with acute leukemia. Other treatment options for MRD, especially in the early post-transplantation setting, are limited by ongoing transplantation-related comorbidities. Cytoreductive therapy is generally poorly tolerated; accordingly, all of our patients who received chemotherapy to treat post-transplantation MRD died from treatment-related toxicity.

In light of the limited ability to treat post-transplantation MRD, our study provides further support for the need to improve pretransplantation risk stratification for identifying those patients at greatest risk for relapse in whom early interventions for relapse prevention, such as early withdrawal of immunosuppression or DLI, would be indicated [21,25,39]. Given the important prognostic value of pretransplantation MRD status on post-transplantatin outcomes, specifically in patients with ALL [40], pretransplantation MRD reduction is another strategy that may lead to improved post-transplantation outcomes [21]. Because this patient population has relatively chemotherapy-refractory disease, we now consider referring patients with pretransplantation MRD for novel immunotherapeutic clinical trials for MRD reduction (eg, chimeric antigen receptor therapy, immunotoxin therapy) before HCT in an attempt to improve post-transplant outcomes, an approach that requires further evaluation.

Although pretransplantation MRD positivity is the most strongly predictive factor of post-transplantation relapse [40-42], we do not believe that this factor should preclude proceeding to HCT. Certainly, improved preemptive interventions may reduce the risk of relapse in those with pretransplantation MRD. In our cohort, among the patients who received myeloablative conditioning and were in a morphological remission, 10 of 35 patients (28.5%) who were MRD negative and 11 of 22 patients (50%) who were MRD positive experienced relapse (Table 2). Consistent with other studies [28], patients with pretransplantation MRD had a higher rate of relapse, but many were able to experience disease-free survival, with a lower prognostic value of pretransplantation MRD in patients with AML compared with those with ALL.

The main limitation of our study is its retrospective design incorporating a heterogeneous patient population, including higher-risk patients with refractory disease and/or those who received nonmyeloablative/reduced-intensity pretransplantation conditioning. Similar findings were seen in patients who were in remission and received myeloablative conditioning, however. In addition, the limited sensitivity of our AML flow cytometry MRD might have missed very low levels of MRD before overt relapse, biasing more of the patients with AML to present at a state of higher disease burden, when intervention was less effective. Certainly, ongoing development focused on optimizing evaluation of AML MRD should be implemented to improve the ability of disease detection to attempt early preemptive intervention for relapse prevention [42-44].

In conclusion, our results illustrate the challenges in treating post-transplantation MRD for relapse prevention in patients with acute leukemia. The primary challenge lies in the fact that most patients who relapse may already be in a state of overt relapse at the time of disease detection. Our results do not indicate a survival advantage for those with relapse detected at the stage of MRD. Whether more frequent or more sensitive measures of disease evaluation in the early post-transplantation period to potentially identify an even lower degree of MRD or detect disease before overt relapse would lead to improved outcomes merits further exploration. Nonetheless, post-transplantation intervention may still be limited by the early timing of relapse and/or rapid disease progression. Given the poor outcomes once post-transplantation disease is detected, improved pretransplantation risk stratification and a shift of focus to relapse prevention are needed to improve post-transplantation outcomes.

Table 3
Outcomes of Patients with Leukemia and Post-HCT MRD

Patient	Disease	Pre-HCT Disease Status	Conditioning	Donor	Days from HCT to Detection of Post-HCT MRD	% MRD*	Mode of Detection	Days from HCT to Overt Relapse	Days from HCT to First Intervention	Intervention	Survival after HCT, d	Cause of Death	Disease Status at Last Evaluation
2	ALL	+BCR-ABL 0.01% by RT-PCR only, flow negative	MA (Cy/TBI)	MSD	60	0.01	Flow cytometry and cytogenetics, + BCR-ABL PCR	84	90	Chemo	115	Multiorgan failure	PD
6	ALL	0.29% MRD by flow	MA (Cy/TBI)	MSD	56	0.01	Flow cytometry	NA	70	DLI	83	CMV pneumonia, ARDS	None performed before death
76	ALL	+BCR-ABL 0.03% by RT-PCR only, flow negative	NMA	Haploidentical	35	BCR-ABL detection by RT-PCR, non-quantifiable	Cytogenetics	Increasing copies of BCR-ABL without overt relapse	No treatment initiated due to ongoing toxicities post-HCT	NA	153	Adenovirus, pulmonary hemorrhage, fungal infection	CR
46	AML	MRD-negative CR	NMA	Haploidentical	30	0.08	Cytogenetics	51	30†	WIS→2nd HCT	247	Multiorgan failure, GVHD, sepsis	CR
49	AML	1% by flow	NMA	Haploidentical	29	3	Flow cytometry	50	52	Chemo + DLI	81	Sepsis	PD
63	AML	Refractory disease	MA (Bu/Cy)	MUD	64	1	Flow cytometry	77	69†	WIS→ Chemo	138	Sepsis	PD
65	AML	Refractory disease, CNS negative	MA (Bu/Cy)	MUD	28	2-3	Flow cytometry	45	29†	WIS→ Chemo	150	VOD, GVHD	PD

HCT indicates hematopoietic stem cell transplantation; MRD, minimal residual disease; ALL, acute lymphoblastic leukemia; BCR-ABL, tyrosine kinase gene; RT-PCR, reverse-transcriptase polymerase chain reaction; MA, myeloablative; Cy, cyclophosphamide; TBI, total body irradiation; MSD, matched sibling donor; CMV, cytomegalovirus; ARDS, acute respiratory distress syndrome; NMA, nonmyeloblative; AML, acute myelogenous leukemia; WIS, withdrawal of immunosuppression; GVHD, graft-versus-host disease; PD, progressive disease; Bu, busulfan; DLI, donor lymphocyte infusion; Chemo, chemotherapy; VOD, veno-occlusive disease; MUD, matched unrelated donor; CNS, central nervous system.

* Indicates the level of disease detected at the first evidenceof MRD; specifically, for those patients who presented at days 56, 60, and 64, previous disease restaging at 1 month post-HCT was negative.

† Indicates that therapy was initiated before overt relapse.

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